DOI: 10.1111/all.14194

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

LETTER TO THE EDITOR

Unraveling the complexity of atopic dermatitis: The CK-CARE approach toward precision medicine

To the editor,

Although clinicians acknowledge the phenotypic heterogeneity of atopic dermatitis (AD), its current management remains a "one-size-fits-all" approach. Even the newest approved medicinal products and those in the pipeline ground on the assumption of a single or dominant underlying mechanism which are mainly based on two pillars: (a) intrinsically disturbed epidermal barrier function as the result of numerous candidate genes related to the biochemical structure of the epidermis such as Filaggrin-1 or 2, Claudin-1, and many others; (b) the assumed dominant T2 type of immune response locally mainly involving IL-13 and IL-31.

Recent reports exploring the immunologic background unraveled different immune responses in various ethnic populations[1] and between pediatric and adult patients.[2] We begin to understand the mechanisms behind the complexity of AD. Substantial hurdles in translating this emerging knowledge into personalized prevention and therapeutic strategies toward precision medicine remain.[3] Overcoming these hurdles is a major task for academic research which has access to large and representative cohorts. In this letter, (a) we expose the gaps in our understanding of the complexity of AD and (b) describe the approach chosen by the Christine Kühne-Allergy Research and Education (CK-CARE) program.

Critical questions need to be addressed in systematic approaches to improve our understanding of the complexity of AD:

- Is the epidermal barrier dysfunction or rather the disturbed immune response more relevant for triggering the first lesions in infancy, childhood or adults?
- The mechanisms underlying the various AD onsets remain elusive.[4] Did the patients with late onset (=adult onset) or very late onset (older than 60 years) have AD in infancy/childhood? The concept of AD as a "dormant disease," that is, individuals who reported to have had AD in childhood or adulthood and in whom the disease has not shown any sign of activity for more than 10 years, needs to be explored.
- The functional genomics beyond dry and sensitive skin remains mysterious. The consequences for the trans-epidermal IgE-sensitization need to be addressed.
- The role of visible and subclinical inflammation and their systemic impact remain an unsolved issue.
- The mechanisms leading to "atopic march" and nonatopic comorbidities are enigmatic.[5]
- *Staphylococcus aureus*-dominated skin dysbiosis has been investigated in sophisticated studies, but the chicken or egg question remains. Does the dysbiosis play a role in infancy while being an epiphenomenon later on?[6]
- The role of IL-4 and IL-13 is assumed to be essential.[7] More recent findings point to a sequence of mechanisms also involving IL-17 and IL-22. This impacts on the development of innovative therapies targeting pivotal structures with biologics, small molecules, or protein-protein interaction modulators (PPIMs).
- The adaptive immunity undergoes an initial "learning phase" in infancy/early childhood offering a window of opportunity for intervention. It is unclear which children would benefit from this strategy to prevent AD and stop the "atopic march."
- The role of IgE and the concept of extrinsic/intrinsic AD remain elusive. Should we revise this dogma based on an arbitrary definition of total serum IgE levels?
- SCORAD, EASI, and vIGA-AD are validated tools and mandatory for regulatory purposes, but the thresholds for severity grades are arbitrary. What is the scientific rationale for the current definition of mild, moderate, and severe?
- How do environmental factors impact on the "atopic march"? Which factors will skew the immune system toward a proallergic/T2 immune response?[8]
- Psychosocial factors may play a role in the development of allergic diseases.[9] Do (psycho)social factors affect AD severity via psychoneuroimmunologic or behavioral pathways?

In a joint academic effort to address these gaps, a unique patient-centric project was started with the support of the Kühne Foundation: The CK-CARE registry and biobank program with currently more than 1200 patients recruited under real-world conditions.

The CK-CARE program aims (a) to explore the mechanisms underlying the heterogeneity of AD and its various trajectories; (b) to identify and validate biomarkers of different values (diagnostic, prognostic, predictive, etc) for patient stratification in patient care, clinical trials, and research projects[10]; (c) to identify new potential drug targets; (d) to collect and learn from real-world data; and (e) to

develop and provide tools for drug development programs in the era of precision medicine.

The CK-CARE program combines several crucial features (see Figure 1):

- The diversity of recruited patients: from newborns to very old patients with active AD of any severity or in remission. As controls, following population will also be included: nonatopic individuals (based on personal family history) (n = 200), atopic individuals with asthma and/or rhinitis but never had AD (n = 100); patients suffering from psoriasis (n = 100) and patients with "dormant AD" (as defined above) (n = 100).
- Detailed phenotypic information including severity scoring (SCORAD and EASI), atopy stigmata, patient-related outcomes, comorbidities, psychosocial aspects, etc.
- A comprehensive collection of epidemiological data including detailed information on the family history, the course of the disease, diet habits, current and past therapies, etc.
- Collection of biomaterials including swabs for microbiomics, serum samples, peripheral blood cells, genomic DNA, and skin biopsies.
- All the biomaterials are stored in duplicate at the recruitment site and at the central biobank facility (CK-CARE headquarter at the campus in Davos, Switzerland).
- Photographic documentation.
- The patients are followed with one visit per year for at least 5 years.

Based on this platform, the CK-CARE research program will be able to address many important gaps, some of them being listed below:

- Its birth cohort will provide in-depth information on the individual trajectories of AD, their immunological kinetics, the emergence of comorbidities. The identification of a window of opportunity for prevention and therapeutic interventions in high-risk populations defined by biomarkers.
- The follow-up approach will enable us to explore the immune response and the skin microbiome in different age ranges as well as during childhood when the remission phase is expected to occur.
- Individuals in long-term remission will deliver insight into the immunologic status in this phase.
- The reactivation of AD in older patients (concept of "dormant disease") and the role of environmental factors will be explored in a retrospective and prospective manner.
- The inclusion of patients with late/very late onset provides crucial insights in this ill-defined phenotype and helps to define phenotype- and endotype-based diagnostic criteria for older patients.

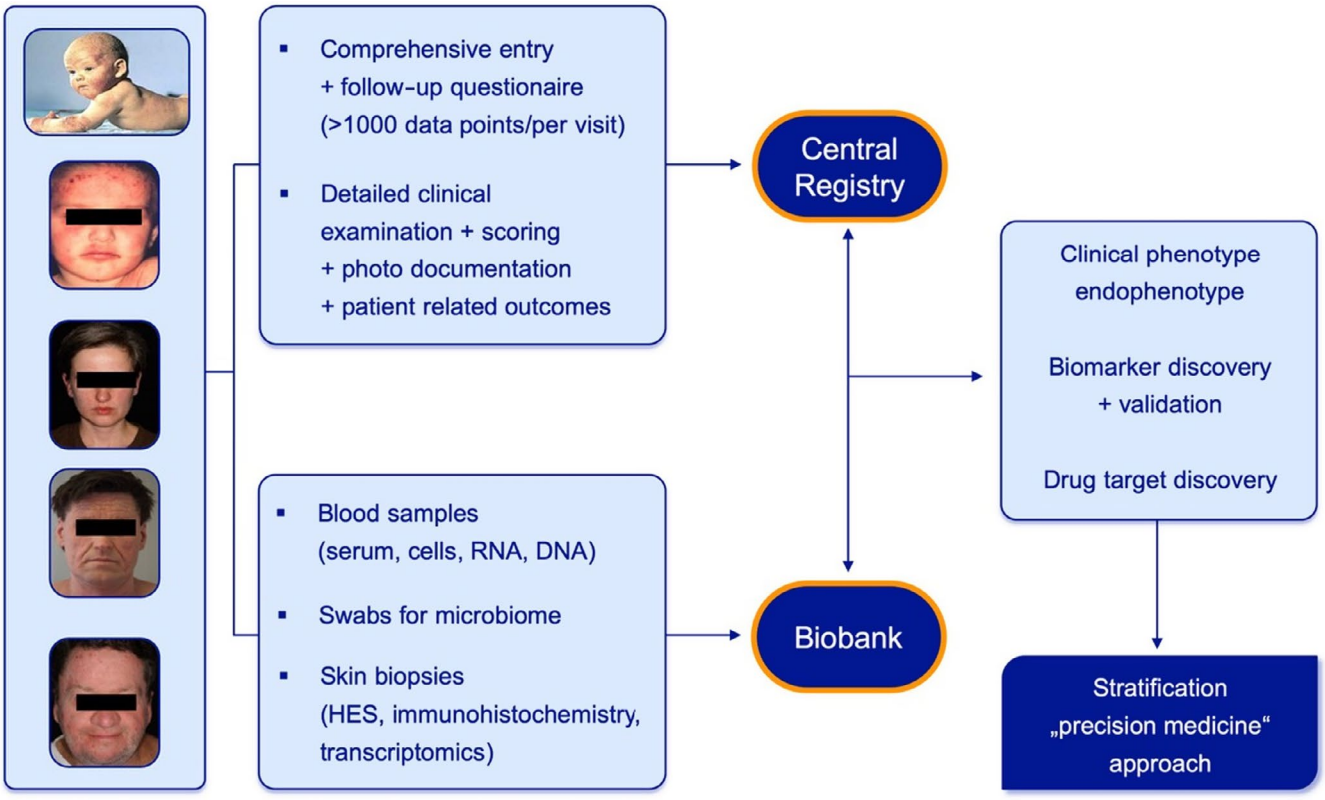

FIGURE 1 Schematic representation of the information and materials collected by the CK-CARE program in the consortium centers in Bonn and Augsburg (Germany), in Zürich, St. Gallen and medical campus in Davos (Switzerland). About 1000 data points on epidemiologic and phenotypic information are collected per patient at each visit. The follow-up study is planned for at least 5 y. All procedures are codified according to SOP and subjected to quality control

- The immunological analysis of the late/very late onset or reactivation will provide key information on the potential role of systemic inflammation in the emergence of atopic/nonatopic comorbidities and the benefit of targeted therapies in a biomarker-based stratification of AD patients.

We are far from understanding the mechanistic complexity of the AD puzzle. With the analysis of comprehensive sets of patient information and biomaterial, the CK-CARE program will contribute to the discovery and validation of relevant biomarkers and pave the way to precision medicine in AD.

FUNDING INFORMATION

This study was supported by the Christine Kühne—Center for Allergy Research and Education (CK-CARE).

CONFLICT OF INTEREST

TB reports personal fees from Sanofi/Genzyme/Regeneron, AbbVie, Allmiral, AnaptysBio, Arena Pharma, Asana Biosciences, Böhringer-Ingelheim, Celegne, Dermavant, DermTreat, FLX Bio, Galapagos, Galderma, GSK, Incytes, Kymab, LEO, Lilly, MenloTx, Novartis, Pfizer, UCB, and Vectans. C T-H has received grants or personal fees from Sanofi Genzyme, Töpfer, Sebapharma, Novartis, Lilly Pharma, Danone Nutricia, outside the submitted work. GS has no conflict of interest to declare.RL is part of the advisory board of Pfizer, Vifor, AstraZeneca, Milupa, Sanofi Genzyme, Menarini, and has received fees for a talk in the Forum für Medizinische Fortbildung. CA declares research funding from Allergopharma, Idorsia, Swiss National Science Foundation, European Commission's Horizon 2020 Framework Programme (Cure), Novartis Research Institutes, AstraZeneca, Scibase, and Sanofi Aventis Regeneron. P S-G reports grants or personal fees from AbbVIe, Astra Zeneca, BioMed, Eli Lilly, Galderma, GSK, LEO, Novartis, Pfizer and Sanofi/Genzyme/Regeneron.

KEYWORDS

atopic dermatitis, endotypes, phenotype, precision medicine

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